REMARKS

Reconsideration of this application, as amended, is respectfully requested.

A. Cross-reference to related applications

The Applicants wish to draw the Examiner's attention to the Applicants' related co-pending applications and issued patents (see Appendix A) directed to nanoparticles and methods of preparation and use thereof.

B. Status of the claims

Claims 433-437 and 439-446 were pending in this application. New claims 447-494 were added to further clarify the invention. Support for the new claims can be found in the specification, for instance, on page 55, line 8-page 57, line 14; page 106, line 25 to page 108, line 24; and Figure 21. Accordingly, no new matter has been added to this application as a result of this amendment. Claims 433-437, 439-446, and 447-494 are now pending in this application.

C. Double patenting rejection

Claims 433-437 and 439-446 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 237-265 of co-pending application no. 09/975,376 and claims 433, 446, and 461-474 of co-pending application no. 09/975,059. A terminal disclaimer is attached. Accordingly, withdrawal of the rejection is in order and is respectfully requested.

D. Rejection under 35 U.S.C. section 102(e) or 103(a) in view of Kossovsky, Kausch, Yguerabide, and Chavany

As a threshold matter, the Federal Circuit has stated that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983).

Likewise, the Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1485 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988).

Contrary to the Examiner's position, the Applicants submit that neither Kossovsky, Kausch, Yguerabide, Chavany, nor Coffer teach or suggest what the Applicants have done. Moreover, the Applicants further submit that neither Kossovsky, Kausch, Yguerabide, Chavany, nor Coffer can be applied in rejecting new method claims 447-494.

1. **Kossovsky**

Claims 433-437 and 439-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Kossovsky et al. (U.S. Patent no. 5,460,831)("Kossovsky"). The Examiner alleged that Kossovsky teaches or suggests the presently claimed composition, relying on the Abstract, cols. 3 and 4, and Examples 1-13 for support. The Applicants respectfully traverse this rejection.

The Applicant respectfully submit that the Examiner's reliance on Kossovsky is misplaced as none of the cited portions of Kossovsky support the Examiner's allegations. Kossovsky merely relates to targeted transfection nanoparticles. See Abstract. Kossovsky also relates to compositions of various nanoparticle cores and use of the cores as transfection agents (see cols 3 and 4). Kossovsky's Examples further relate to methods of preparing and coating the cores with cellobiose, P5P, or citrate films (Examples 1-8, 11) and cleaning the cores (Examples 9 and 10). Examples 12 -14 further relate to absorbing various transfection agents to the cores. For instance, Kossovsky relates to absorbing purified DNA or RNA fragments of the human deaminase gene to coated cores (Example 12), absorbing sonicated viral particles and phospholipids membranes to coated cores (Example 13), and absorbing a human deaminase gene

expression cassette and LDL membrane proteins to the coated cores. Nowhere in Kossovsky's disclosure does he teach or suggest nanoparticles having "at least two types of oligonucleotides attached thereto, the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2, wherein at least one type of oligonucleotides comprises recognition oligonucleotides, the recognition oligonucleotides comprising a recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide". See claim 433. Accordingly, withdrawal of the section 102(e) and/or 103(a) rejection against the claims based on Kossovsky is in order and is respectfully requested. In addition, the Applicants further submit that Kossovsky does not teach or suggest the claimed detection method of new claims 447-494 and thus this reference cannot be applied to support a rejection of the new claims.

2. Kausch

Claims 433-437 and 439-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Kausch al. (U.S. Patent no. 5,665,582)("Kausch"). Specifically, the Examiner alleged that Kausch teaches nanoparticle-oligonucleotide conjugates having the presently recited surface density range, relying on the Abstract, Col. 4-10, 17-19, 24 and Examples 1, 2 and 4-8 for support. The Applicants respectfully traverse this rejection.

Contrary to the Examiner's position, Kausch does not support the Examiner's allegations. Kausch merely relates to a method for isolating biological materials. See Abstract. Kausch first anchors the biological material onto a solid support such as a glass slide or coverslip. The anchored biological material is then labeled with a binding composition and magnetic particles. The labeled biological material is then released from the support and the release material is then sorted by a magnetic force. The Examiner's cited passages of the Kausch support the aforementioned method. See abstract and cols. 4-10, particularly col. 6, lines 24-44 and col. 9, lines 44 to col. 10, line 16. Example 1 described isolation and anchoring of mouse DNA onto glass coverslips and use of magnetic particles to sort out the DNA. See col. 28, line 51 to col. 29, line 3. Example 2 also described anchoring chromosomes onto an alginate cushion, followed by detachment of the chromosomes and sorting using magnetic particles. Examples 4 (col. 39 –

use of magnetic particles for sorting), 5 (col. 44 – preparation of magnetic particles), 6 (cols. 44 and 45 – conventional flow cytometry), 7 (cols. 45-50 – anchoring biological material to support, detachment of biological material from support, and sorting by magnetic particles) and 8 (cols. 50-52 – anchoring biological material to support, detachment of biological material from support, and sorting by magnetic particles). Nowhere in Kausch's disclosure does he teach or suggest nanoparticles having "at least two types of oligonucleotides attached thereto, the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2, wherein at least one type of oligonucleotides comprises recognition oligonucleotides, the recognition oligonucleotides comprising a recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide". See claim 433. Accordingly, withdrawal of the section 102(e) and/or 103(a) rejection against the claims based on Kausch is in order and is respectfully requested. In addition, the Applicants further submit that Kausch does not teach or suggest the claimed detection method of new claims 447-494 and thus this reference cannot be applied to support a rejection of the new claims.

3. **Yguerabide**

Claims 433-437 and 439-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Yguerabide (U.S. Patent No. 6,214,560)("Yguerabide"). The Applicants respectfully traverse this rejection.

Specifically, the Examiner alleged that Yguerabide taught detection and measurement of one or more analytes in a sample using particles of specific composition and size using light scattering. The discussion is found starting in col. 82, line 35, of Yguerabide. Col. 83 provides further discussion regarding particle size and particle binding to a surface. Cols. 77-80 relate to particles and their preparation. Col. 110 (Example 32) relates to a nucleic acid labeled particle but does not provide or suggest any particle surface density. Furthermore, surface density cannot be calculated since Yguerabide does not provide any DNA concentration. There is no discussion or suggestion anywhere in Yguerabide of a nanoparticle having any recognition and/or diluent oligonucleotides and/or particle surface density. The claims recite limitations that are neither taught, made obvious, or suggested by the cited reference. Thus, the Applicant respectfully

submits that Yguerabide cannot be applied to support section 102(e) and/or section 103(a) rejections of the claims. In addition, the Applicants further submit that Yguerabide does not teach or suggest the claimed detection method of new claims 447-494 and thus this reference cannot be applied to support a rejection of the new claims.

4. **Chavany**

Claims 433-437, and 439-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Chavany et al. (Pharmaceutical Research, Vol. 11: pp. 1370-1378)("Chavany"). Specifically, the Examiner alleged that Chavany teaches nanoparticle-oligonucleotide conjugates having the recited surface density, relying on pages 1370-1372, 1375 and 1377 for support. The Applicants respectfully traverse this rejection.

Contrary to the Examiner's position, none of the cited passages in Chavany support the Examiner's position. Chavany merely relates to the preparation of transfection nanoparticles that are resistant to nuclease degradation and that have increased cellular uptake. The transfection nanoparticles are formed by the absorption of oligonucleotides onto the nanoparticles. See Abstract and page 1371 under "Absorption of oligonucleotides to PIHCA nanoparticles". However, Chavany does not describe any nanoparticle size range and thus surface density of oligonucleotides on the nanoparticle surface cannot be readily determined. Nowhere in Chavany's disclosure does she teach or suggest nanoparticles having "at least two types of oligonucleotides attached thereto, the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2, wherein at least one type of oligonucleotides comprises recognition oligonucleotides, the recognition oligonucleotides comprising a recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide". See claim 433. Accordingly, withdrawal of the section 102(e) and/or 103(a) rejection against the claims based on Chavany is in order and is respectfully requested. In addition, the Applicants further submit that Chavany does not teach or suggest the claimed detection method of new claims 447-494 and thus this reference cannot be applied to support a rejection of the new claims.

E. Rejection under 35 U.S.C. section 102(b) in view of Coffer

Claims 433-436, 439-442, and 444-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Coffer et al. (Nanotechnology, Vol. 3, lines 69-76 (1992))("Coffer"). The Examiner alleged that Coffer teaches a nanoparticle-oligonucleotide conjugate having the presently recited surface density, relying on pages 69-72 and 75 for support. The Applicants respectfully traverse this rejection.

Contrary to the Examiner's position, Coffer does not support the Examiner's allegations. Coffer merely relates to CdS nanocrystallites stabilized by DNA and describes a two-step procedure of first mixing cadium ions with DNA to form a solution and adding sulfide to the solution to make a CdS cluster. See page 70-71. The DNA merely serves as a template for the formation and stabilization of CdS clusters. See page 71. While Coffer does mention the DNA concentration used in the solution for generating the CdS clusters, Coffer is completely silent with respect to the specific surface density of DNA at the surface of any nanoparticles. Indeed, nowhere in Coffer's disclosure does he teach or suggest nanoparticles having "at least two types of oligonucleotides attached thereto, the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2, wherein at least one type of oligonucleotides comprises recognition oligonucleotides, the recognition oligonucleotides comprising a recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide". See claim 433. Accordingly, withdrawal of the section 102(e) and/or 103(a) rejection against the claims based on Coffer is in order and is respectfully requested. In addition, the Applicants further submit that Coffer does not teach or suggest the claimed detection method of new claims 447-494 and thus this reference cannot be applied to support a rejection of the new claims.

F. Conclusion

In conclusion, the Applicants respectfully submit that the claims in this application are in allowable condition and request a Notice to this effect.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes that this would be helpful in expediting the prosecution of this application.

Respectfully submitted,

Dated: Oct. 29, 2004

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APPENDIX A

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
00-653-G	U.S. 10/794,741 Filed 3/5/04	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton, Garamella, Li, Park/ NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFORE	PENDING
00-713-B1	09/923,625 Filed 8/7/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	U.S. Patent no. 6,773,884, issued 8/10/04
00-713-C	09/344,667, filed 6/25/99	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFORE	U.S. Patent No. 6,361,944, issued 3/26/02
00-713-I	U.S.S.N 09/603,830 Filed 6/26/00	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton; NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	U.S. Patent No. 6,506,564, issued 1/14/03
00-713-I-1	09/961,949 9/20/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton;	U.S. Patent No. 6,582,921, issued June 24, 2003

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
		NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	
00-713-I-2	09/957,318 9/20/01	See 00-713-I-1	U.S. Patent No. 6,759,199, issued 7/6/04
00-713-I-3	09/957,313 9/20/01	See 00-713-I-1	U.S. Patent No. 6,645,721, issued 11/11/03
00-713-I-4	09/966,491 9/28/01	See 00-713-I-1	U.S. Patent No. 6,610,491, issued August 26, 2003
00-713-I-5	09/966,312 9/28/01	See 00-713-I-1	U.S. Patent No. 6,673,548, issued January 6, 2004
00-713-I-6	09/967,409 9/28/01	See 00-713-I-1	U.S. Patent No. 6,740,491, issued May 24, 2004
00-713-I-7	09/974,500 10/10/01	See 00-713-I-1	U.S. Patent No. 6,709,825, issued March 23, 2004
00-713-I-8	09/974,007 10/10/01	See 00-713-I-1	PENDING
00-713-I-9	09/973,638 10/10/01	See 00-713-I-1	ALLOWED
00-713-I-10	09/973,788 10/10/01	See 00-713-I-1	U.S. Patent No. 6,720,411, issued April 13, 2004
00-713-I-11	09/975,062 10/11/01	See 00-713-I-1	U.S. Patent No. 6,677,122, issued January 13, 2004
00-713-I-12	09/975,376 10/11/01	See 00-713-I-1	PENDING
00-713-I-13	09/975,384 10/11/01	See 00-713-I-1	PENDING

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
00-713-I-14	09/975,498 10/11/01	See 00-713-I-1	ALLOWED
00-713-I-15	09/975,059 11/11/01	See 00-713-I-1	ALLOWED
00-713-I-16	09/976,601 10/12/01	See 00-713-I-1	ALLOWED
00-713-I-17	09/976,968 10/12/01	See 00-713-I-1	ALLOWED
00-713-I-18	09/976,971 10/12/01	See 00-713-I-1	U.S. Patent No. 6,682,895, issued 1/27/04
00-713-I-19	09/976,863 10/12/01	See 00-713-I-1	PENDING
00-713-I-20	09/976,577 10/12/01	See 00-713-I-1	U.S. Patent No. 6,720,147, issued April 13, 2004
00-713-I-21	09/976,618 10/12/01	See 00-713-I-1	U.S. Patent no. 6,812,334, issued Nov. 2, 2004
00-713-I-22	09/981,344 10/15/01	See 00-713-I-1	U.S. Patent No. 6,777,186, issued August 17, 2004
00-713-I-23	09/976,900 10/12/01	See 00-713-I-1	ALLOWED
00-713-I-24	09/976,617 10/12/01	See 00-713-I-1	U.S. Patent No. 6,730,269, filed May 4, 2004
00-713-I-25	09/976,378 10/12/01	See 00-713-I-1	PENDING
00-713-i-26	10/410,324 04/10/03	See 00-713-I-1	PENDING
00-713-L	U.S.S.N. 09/693,005	Mirkin, Letsinger, Mucic, Storhoff,	U.S. Patent No. 6,495,324, issued

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
	Filed 10/20/00	Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFORE	12/17/02
00-713-M	U.S.S.N. 09/693,352 Filed 10/20/00	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFORE	U.S. Patent No. 6,417,340, issued 7/9/02
00-714-G	U.S. 09/830,620 Filed 8/15/01	Mirkin, Nguyen/ NANOPARTICLES WITH POLYMER SHELLS	PENDING
00-715-A	U.S. 09/760,500 Filed 1/12/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton; Garamella, Li/ METHOD OF ATTACHING OLIGONUCLEOTIDES TO NANOPARTICLES AND PRODUCTS PRODUCED THEREBY	U.S. Patent No. 6,767,702, issued July 27, 2004
00-715-B	U.S. 10/716,829 Filed 11/18/03	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton; Garamella, Li/ METHOD OF ATTACHING OLIGONUCLEOTIDES TO NANOPARTICLES AND PRODUCTS PRODUCED THEREBY	Pending

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
00-1085-A	U.S.S.N. 09/820,279 Filed 3/28/01	Mirkin,Letsinger, etc./ METHOD AND MATERIALS FOR ASSAYING BIOLOGICAL MATERIALS	U.S. Patent No. 6,750,016, issued June 15, 2004
00-1085-G	U.S.S.N. 10/640,618 Filed 8/13/03	Mirkin,Letsinger, etc./ METHOD AND MATERIALS FOR ASSAYING BIOLOGICAL MATERIALS	Pending
00-1086-A	U.S. 09/903,461 Filed 7/11/01	Letsinger, Garimella/ METHOD OF DETECTION BY ENHANCEMENT OF SILVER STAINING	U.S. Patent No. 6,602,669, Filed 8/5/03
00-1272-C	U.S.S.N. 10/008,978 Filed 12/7/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton, Garimella, Li, Park, Lu/ NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREOF	ALLOWED
01-565-A	USSN 10/125,194 Filed 4/18/02	Mirkin, Nguygen, Watson, Park/ OLIGONUCLEOTIDE-MODIFIED ROMP POLYMERS AND CO-POLYMERS	PENDING
01-599-A	U.S.S.N. 10/291,291 Filed 11/08/02	Storhoff/NOVEL THIOL-BASED METHOD FOR ATTACHING OLIGONUCLEOTIDES TO NANOPARTICLES	PENDING
01-661-A	U.S.S.N.	Mirkin, Cao, Jin/	PENDING

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
	10/034,451 Filed 12/28/01	DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	
01-661-C	U.S.S.N. 10/153,483 Filed 5/22/02	Mirkin, Cao, Jin/ DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	PENDING
01-661-E	U.S.S.N. 10/397,579 3/26/03	Mirkin, Cao, Jin/ DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	PENDING
01-1565-A	U.S.S.N. 10/266,983 Filed 10/08/02	Park, Taton, Mirkin/ARRAY-BASED ELECTRICAL DETECTION OF DNA USING NANOPARTICLE PROBES	PENDING
01-1633-A	U.S.S.N. 10/266,983 Filed 10/8/02	Park, Taton, Mirkin/NANOPARICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	PENDING
01-1705-A	U.S.S.N. 10/108,211 Filed 3/27/02	Nam, Park, Mirkin/BIO-BARCODES BASED ON OLIGONUCLEOTIDE-MODIFIED NANOPARTICLES	PENDING
02-338-B	USSN 10/172,428 Filed 6/14/02	Cao, Jin, Nam, Mirkin/MULTICHANNEL DETECTION USING NANOPARTICLE PROBES WITH RAMAN SPECTROSCOPIC	PENDING

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
		FINGERPRINTS	
02-338-C	10/431,341 5/7/03	Cao, Jin, Nam, Mirkin/MULTICHANNEL DETECTION USING NANOPARTICLE PROBES WITH RAMAN SPECTROSCOPIC FINGERPRINTS	PENDING
02-1227-A	10/735,357 Filed 12/12/03	DIRECT SNP DETECTION WITH UNAMPLIFIED NUCLEIC ACID USING NANOPARTICLE PROBES	PENDING
03-214-A	10/789,831 Filed 2/27/04	LABEL-FREE GENE EXPRESSION PROFILING WITH UNIVERSAL NANOPARTICLE PROBES IN MICROARRAY ASSAY FORMAT	PENDING
03-466-C	10/854,848 Filed 5/27/04	METHOD FOR DETECTING ANALYTES BASED ON EVANESCENT ILLUMINATION AND SCATTER-BASED DETECTION OF NANOPARTICLE PROBE COMPLEXES	PENDING
03-666-E	10/877,750 Filed 6/25/04	BIOBARCODE	PENDING